Part I Overview Information

Department of Health and Human Services

Participating Organizations
National Institutes of Health (NIH), (http://www.nih.gov/)

Components of Participating Organizations
National Heart, Lung, and Blood Institute (NHLBI), (http://www.nhlbi.nih.gov/)
National Center on Sleep Disorders Research (NCSDR), (http://www.nhlbi.nih.gov/about/ncsdr/index.htm)
National Institute on Aging (NIA), (http://www.nia.nih.gov/)
National Institute on Alcohol Abuse and Alcoholism (NIAAA), (http://www.niaaa.nih.gov/)
National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), (http://www.niams.nih.gov/)
National Cancer Institute (NCI), (http://www.nci.nih.gov/)
National Institute of Child Health and Human Development (NICHD), (http://www.nichd.nih.gov/)
National Center for Complementary and Alternative Medicine (NCCAM), (http://www.nccam.nih.gov/)
National Institute on Drug Abuse (NIDA), (http://www.nida.nih.gov/)
National Institute of Mental Health (NIMH), (http://www.nimh.nih.gov/)
National Institute of Neurological Disorders and Stroke (NINDS), (http://www.ninds.nih.gov/)
National Institute of Nursing Research (NINR), (http://ninr.nih.gov/ninr/)
Office of Research on Women's Health (ORWH), (http://www4.od.nih.gov/orwh/)

Title: Research on Sleep and Sleep Disorders

Announcement Type
This is a reissue of PA-95-014, which was previously released December 23, 1994

Program Announcement (PA) Number: PA-05-046

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Application Receipt Dates(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Peer Review Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Council Review Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Earliest Anticipated Start Date: http://grants.nih.gov/grants/funding/submissionschedule.htm
Expiration Date: June 1, 2008

Due Dates for E.O. 12372
Not Applicable

Additional Overview Content

Executive Summary

- As summarized in the 2003 National Sleep Disorders Research Plan (http://www.nhlbi.nih.gov/health/prof/sleep/res_plan/index.html), multiple scientific areas in sleep and sleep disorders need additional research. In addition, therapy for a number of sleep disorders remains suboptimal, and the research workforce addressing sleep science is insufficient. The NHLBI, National Center on Sleep Disorders Research, and co-sponsoring member Institutes and Centers of the Trans-NIH Sleep Research Coordinating Committee therefore invite submission of grant applications proposing research to advance biomedical knowledge related to sleep or sleep disorders, improve understanding of the neurobiology or functions of sleep over the life-span, enhance timely diagnosis and effective treatment for individuals affected by sleep-related disorders, or implement and evaluate innovative community-based public health education and intervention programs. Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. The total amount awarded and the number of awards will depend upon the mechanism, numbers, quality, duration , and costs of the applications received.

- This PA will use the NIH R01and R21 award mechanisms.
- Eligible organizations include institutions with any of the following characteristics:

  • For-profit or non-profit organizations
  • Public or private institutions, such as universities, colleges, hospitals, and laboratories
  • Units of State and local governments
  • Eligible agencies of the Federal government
  • Domestic or foreign institutions/organizations
  • Faith-based or community-based organizations

- Eligible principal investigators include individual with the skills, knowledge, and resources necessary to carry out the proposed research. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.
- There is no limit on the number of applications that may be submitted.
- One can get application materials at http://grants.nih.gov/grants/forms.htm
- Telecommunications for the hearing impaired is available at: TTY 301-451-0088

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Part II - Full Text of Announcement

Section I. Funding Opportunity Description

1. Research Objectives

The three broad categories of sleep-related problems include:

- **Sleep Restriction:** Many children, adolescents, and adults regularly fail to get sufficient sleep to function effectively during waking hours as a result of imposed or self-imposed lifestyles and work schedules.
- **Primary Sleep Disorders:** More than 70 types of sleep disorders chronically affect people of all ages and their prevalence increases with aging. More than 50% of patients remain undiagnosed and therefore untreated.
- **Secondary Sleep Disorders:** People having a chronic disease, or an alcohol or substance abuse disorder, often experience poor sleep quality and excessive daytime sleepiness. Alterations in circadian rhythmicity and the greater incidence of co-morbid conditions, as well as lifestyle changes, make the aging population at greater risk for sleep disorders.

An estimated 70 million people in the United States suffer from sleep problems, and more than 50% of them have a chronic sleep disorder. About 30 million American adults have frequent or chronic insomnia. Approximately 18 million have sleep apnea (sleep disordered breathing), but fewer than 50% are presently being diagnosed. An estimated 250,000 people have narcolepsy, and 10 to 20% of adults are affected by restless legs syndrome. According to the National Highway Traffic and Safety Administration (NHTSA), 100,000 accidents and 1,500 traffic fatalities per year are related to drowsy driving. More than 50% of Americans over age 65 have sleep difficulties, and prevalence of sleep problems will therefore increase as the over-65 population increases. Each year, s leep disorders, sleep deprivation, and excessive daytime sleepiness add approximately $16 billion annually to the cost of health care in the U.S., and result in $50 billion annually in lost productivity. In addition to conventional therapies to treat sleep disorders, many individuals use complementary and alternative therapies (CAM). According to the 2002 National Health Interview Survey, approximately 1.6 million adults use CAM specifically for sleep disorders. Sleep problems and disorders have major societal impacts, but have not received sufficient attention in basic and clinical research.

The 2003 National Sleep Disorders Research Plan (http://www.nhlbi.nih.gov/health/prof/sleep/res_plan/index.html) summarizes current knowledge regarding the neurobiology of sleep and sleep disorders, and concludes with a prioritized listing of recommendations for future research.

We are now beginning to understand the impact of chronic sleep loss or sleeping at adverse circadian times on the ability to function optimally and on physical and mental health. How sleep loss, sleep displacement (e.g., shift work), and a wide range of sleep disorders affect one's ability to maintain health and healthy functioning in a 24/7 world, however, are relatively poorly understood. In addition, with the enhanced lifespan, the growing aging population carries a risk for sleep disturbances caused by greater physical and psychological changes. Thus, despite substantial scientific progress in both clinical and basic science related to sleep and its disorders, there remains the challenge and the need to better understand the functions of sleep, to better understand and treat disorders affecting sleep, and to explain the nature of human physiology during wakefulness and the individual stages of sleep. Without progress in these areas, millions will continue to suffer the consequences of dysfunction and abuse of this most basic regulatory process.

Sleep Neurobiology:
The discovery of hypocretin/orexin and its role in the development of narcolepsy in animal models and in humans revolutionized our understanding of this debilitating disorder and promises important advances in the diagnosis and therapy of human narcolepsy. However, we need to better understand the neuromodulatory role of hypocretin/orexin and improve our understanding of the basic neurobiological processes that control sleep and wakefulness. New anatomical and physiological approaches have led to advances in our understanding of the location and interconnections between hypothalamic and brainstem circuits controlling REM, nonREM, and wake states. Factors

regulating the activity of these sleep-controlling neurons have been identified. Circuitry and neurotransmitter mechanisms controlling muscle tone across the sleep cycle, of relevance to numerous sleep pathologies, have also been identified.

Circadian Biology:
A growing number of "clock genes" have been identified that play a critical role in mammalian circadian timing. In addition, there is clear evidence that non-suprachiasmatic nucleus (SCN) tissues have clock genes and can demonstrate circadian rhythms. Thus, circadian modulation occurs both centrally and peripherally, further emphasizing the importance of circadian chronobiology in the timing of sleep and waking as well as a wide variety of physiologic functions. These studies of clock genes also apply to humans, in particular patients with advanced sleep phase syndrome, especially prominent in the elderly population. The role of endogenous melatonin in the sleep/wake cycle has been better defined and the clinical studies on the role of exogenous melatonin to treat sleep disorders are ongoing.

Sleep Deprivation:
Previous studies have demonstrated many of the ill effects of total sleep deprivation, but the impact of chronic partial sleep deprivation (restriction) has not been extensively investigated even though it is much more common. Recent studies indicate that 4 to 6 hours of sleep per night yields a progressive, cumulative deterioration in neurobehavioral function including vigilance, neurocognitive performance, and mood. This reduction in performance is also associated with changes in cerebral activation during cognitive tasks. Physiologic changes also appear to occur, e.g., insulin resistance, increased sympathetic activation, decreased immune system function, lower core body temperature, and decreased release of growth hormone. Both the neurocognitive and physiologic effects of chronic sleep loss suggest there is an optimal sleep duration and a cost for failing to achieve it. However, the exact duration of sleep required at different periods of life remains poorly understood, as do the mechanisms driving these neural and metabolic processes.

Sleep-Disordered Breathing (SDB):
The consequences of SDB (obstructive sleep apnea) have become increasingly defined over the last few years. In adults, the contribution of SDB to the development of systemic hypertension is becoming more evident and data are accumulating that other adverse cardiovascular outcomes (stroke, congestive heart failure, myocardial infarction) may result from this disorder. Co-existing obesity can result in structural impairments impacting airway patency, creating additional cardiovascular problems. In children, there is increasing evidence that sleep apnea may contribute to behavioral problems as well as learning and cognitive deficits.

Insomnia:
The high prevalence, risk factors, and consequences of insomnia are being increasingly defined. Insomnia has been identified as a risk factor for the onset of subsequent depression, anxiety, and substance use disorders. In addition, the efficacy and durability of behavioral therapies for insomnia have been demonstrated in controlled clinical trials.

Sleep in Psychiatric, Alcohol, and Substance Use Disorders:
Most psychiatric and substance use disorders are associated with sleep disruption. Alcohol dependence and use of other psychoactive substances lead to complaints of insomnia and sleep disruption that can persist for months into recovery. These sleep disturbances may result in continued alcohol and/or drug use to alleviate symptoms, and thereby precipitate relapse. Psychiatric disorders can also be associated with daytime sleepiness, fatigue, abnormal circadian sleep patterns, disturbing dreams and nightmares. Conversely, increasing evidence suggests that primary insomnia (without concurrent psychiatric disorder) is a risk factor for later developing psychiatric disorders, particularly depression, anxiety, and substance use disorders.

Most progress has been related to associations between psychiatric disorders and various sleep symptoms (e.g., insomnia and nightmares), sleep EEG patterns (e.g., delta EEG activity), and sleep disorders. Less progress has been made in identifying fundamental pathophysiological mechanisms linking psychiatric disorders and sleep. Sensitive and specific sleep biomarkers of psychiatric disorders, for example, have not been validated. Similarly, endogenous circadian rhythm disturbances have not been identified in most patients with depression or other psychiatric disorders. Little is known about characteristics or consequences of sleep disturbances in most childhood psychiatric disorders, in children of alcohol or substance abusing mothers, or in children at high risk for developing psychiatric and alcohol/substance abuse disorders. The application of sleep and circadian rhythm therapies to psychiatric disorders has been limited, and their efficacy not consistently demonstrated.

Clinical neuroscience studies are needed to investigate the common mechanisms and consequences of disordered sleep (e.g., immune dysfunction) in psychiatric and alcohol/substance dependent populations. Insomnia and sleep disturbances are risk factors for psychiatric disorders including alcohol dependence, but long-term follow-up studies have not yet been done to determine whether intervention can reduce these risks and the progression of these disorders.

Pediatrics:
Recent research regarding the physiologic, psychological and developmental aspects of sleep in infants, children, and adolescents has contributed to an increased understanding of the unique aspects of sleep and development. The study of pediatric disorders such as Congenital Central Hypoventilation Syndrome and Rett Syndrome has led to a better basic understanding of autonomic regulation and respiratory control. Recent findings regarding the complex relationship between sleep patterns and hormonal changes in adolescence have broadened our understanding of pubertal influences on sleep and circadian biology. The extent of sleep restriction and sleep disturbances among children and adolescents is much greater than previously believed, and the consequent impact on mood, neurobehavioral and academic functioning, safety, and health is considerable. Recognition of the link between sleep disturbances and neurobehavioral disorders in childhood, such as attention deficit hyperactivity disorder (ADHD), has major public health implications for both the treatment and prevention of psychiatric co-morbidity.

Sleep Education:

A variety of recently implemented educational activities have substantial potential impact on sleep literacy and public health. We need to consolidate and extend the research progress made to date, and to translate new knowledge into effective therapies and community-based dissemination and implementation programs in order to apply what is known to improve public health and quality of life.

Complementary and Alternative Medical Therapies for Sleep Disorders:
Many individuals use c omplementary and alternative medical (CAM) therapies for sleep disorders. These therapies are often already in the public domain, but have only recently been subjected to rigorous basic and clinical research to determine efficacy, effectiveness, and mechanisms of action. Ongoing research is determining efficacy of natural products such as valerian and melatonin for specific sleep disorders. Other CAM approaches such as meditation, yoga, and light therapy are also being investigated for their role in improving sleep. Programs to educate health practitioners about the potential role of evidenced-base CAM therapies for treating sleep disorders will in turn aid in educating the public about both the benefits and risks of CAM therapies.

Sleep in Chronic Pain and Rheumatologic Disorders:
Sleep and changes in sleep are related to various cellular, hormonal, and immunological functions. Pain and other components of disease may influence the sleep process and alter these parameters, thereby interacting with the disease process. Correspondingly, many of the daytime symptoms in patients with rheumatic diseases – pain, stiffness, fatigue, and cognitive dysfunction – may be linked to non-restorative sleep patterns associated with these diseases. Research is needed on the role of sleep, and the bi-directional interactions between sleep and disease processes, in rheumatic diseases in humans and animal models. Studies on effects of sleep and sleep dysfunction on relevant physiological processes, and on disease progression, symptoms, and daily functioning are needed. Effects of disease treatment (e.g., TNF alpha) on sleep should be investigated. In addition, changes in disease-relevant parameters following intervention studies targeting sleep or experimental manipulation of sleep should be investigated, as should the relationship between sleep and pain, especially in fibromyalgia.

Topics for research that would be responsive to this PA include, but are not limited to:

Neurobiology and functions of sleep and neurochemistry of sleep/wake generating systems from fetal life across the full age spectrum, including molecular, biochemical, anatomic and physiologic investigations.

Exploration of the physiologic basis for the restorative function of sleep in maintenance of health.

Basic research on hypocretins to better define the exact role of this system in the regulation of normal sleep and other behaviors.

Neurobiological mechanisms of the effects of sleep, circadian regulation, sleep homeostasis, and sleep disorders on the aging process and the diseases associated with late age.

Methods to measure sleep, circadian physiology, and sleepiness across the age spectrum, including methods used in the home.

Psychological, behavioral , neurobiological, and physiological consequences and underlying mechanisms of long-term partial sleep deprivation from childhood through old age.

Recovery patterns following chronic partial sleep loss and whether rates of recovery vary by age and/or for physiological, behavioral and cognitive processes; identification of factors that facilitate recovery and minimize long-term adverse consequences.

Epidemiologic, behavioral, physiologic or neurobiological studies addressing relationships between the processes of sleep and the development and progression of both neural and non-neural diseases.

Studies of the mechanisms by which sleep disturbances affect adherence to treatments for chronic disease and ways that improving sleep may improve treatment outcomes.

Improved understanding of the processes that lead to specific sleep disorders in infants, children, and adults, including the aged population.

Interventions to help children and adults adapt to the sleep disturbance associated with homes, hospitals, critical care settings, and nursing homes

Studies of sleep disturbance in children and adolescents as a risk factor for the early onset of drinking, and the development of alcohol abuse and dependence.

Studies of insomnia and hypersomnia as modifiable risk factors for poor outcomes in mood, anxiety, and psychotic disorders, alcoholism, and substance abuse disorders, including whether interventions can prevent progression of these disorders and reduce risk for relapse in the alcohol and substance abuse disorders.

Impact of sleep-disordered breathing (SDB) and its treatment on functional status, psychiatric disorders, neurocognitive function and behavior, and other disease processes.

Studies of disorders leading to hypersomnolence or neural mechanisms leading to hypersomnolence in conditions such as narcolepsy or primary central nervous system hypersomnolence, and how these mechanisms may differ from or resemble the effects of sleep loss.

Studies of normal human sleep phenotypes and the normal range of variation in children, adults and the aged (including racial and ethnic disparities), and quantitative assessment of sleep variables such as duration, sleep stage distribution and sleep quality.

Studies of sleep problems and disorders in children related to chronic maternal use of alcohol, cigarette smoking, and narcotic drugs.

Interrelationships between sleep and neuroendocrine systems, including aging male and female populations.

Studies of the role of cytokines in sleep regulation in psychiatric populations also at risk for infectious or inflammatory disorders, and studies of cytokine antagonists in sleep-disturbed alcohol using populations with evidence of immune activation.

New treatments for sleep disorders, including methods to adapt these therapies to individual patients using approaches such as pharmacogenetics.

Basic and clinical research on complementary and alternative medicine (CAM) therapies for sleep disorders. These could include, but are not limited to mind/body therapies such as yoga and meditation; biological based therapies such as herbal medicine; manipulative therapies such as chiropractic manipulation; energy medicine such as Reiki and Qi gong; and therapies based on traditional medical systems such as Traditional Chinese Medicine or naturopathic medicine.

Assessment of outcomes of sleep disorder therapies, including CAM therapies, at all levels including efficacy, adherence, effectiveness, morbidity, quality of life, health care costs, safety, and performance/productivity.

Impact of sleep educational programs related to healthy sleep habits and sleep literacy or to improved rates of diagnosis and treatment of sleep disorders.

Assessment of physician and other health care provider knowledge of sleep disorders and current treatment options, both CAM and conventional.

Applications of informatics to clinical, neurophysiologic, imaging, and genetic studies as they apply to sleep and its disorders.

Neurophysiology of sleep regulation affecting risk for and mechanisms of sleep disorders in women in relation to menarche, pregnancy, or menopause.

N europhysiological and neuroanatomical correlates and gene-environment interactions contributing to racial and ethnic disparities in prevalence and severity of individual sleep disorders, and strategies to better inform racial and ethnic minority populations about sleep-related conditions through public health education programs.

Sleep in neurodegenerative disorders including but not restricted to Parkinson's disease.

Sleep in neuropathic pain conditions.

See Section VIII, Other Information - Required Federal Citations, for policies related to this announcement.

Section II. Award Information

1. Mechanism(s) of Support

This funding opportunity will use the NIH R01 and R21 award mechanism(s). As an applicant, you will be solely responsible for planning, directing, and executing the proposed project.

This funding opportunity uses just-in-time concepts. It also uses the modular as well as the non-modular budget formats (see http://grants.nih.gov/grants/funding/modular/modular.htm). Specifically, if you are submitting an application with direct costs in each year of $250,000 or less, use the modular budget format described in the PHS 398 application instructions. Otherwise follow the instructions for non-modular research grant applications.

2. Funds Available

The total amount to be awarded and the anticipated number of awards will depend upon the quality of the applications received. For R21 awards, you may request a project period of up to two years with a combined budget for direct costs of up $275,000 for the two year

period. For example, you may request $100,000 in the first year and $175,000 in the second year. Normally, no more than $200,000 may be requested in any single year. For information on R21 mechanism, see http://grants.nih.gov/grants/guide/pa-files/PA-03-107.html. For R01 awards, Applications requesting $500,000 or more in direct costs for any year must contact Institute or Center program staff before submitting the application. The applicant must obtain agreement from Institute/Center staff that the Institute or Center will accept the application for consideration for award. For further information, see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

Because the nature and scope of the proposed research will vary from application to application, it is anticipated that the size and duration of each award will also vary. Although the financial plans of the IC(s) provide support for this program, awards pursuant to this funding opportunity are contingent upon the availability of funds and the receipt of a sufficient number of meritorious applications.

Facilities and administrative costs requested by consortium participants are not included in the direct cost limitation, see http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-004.html.

Section III. Eligibility Information

1. Eligible Applicants

1.A. Eligible Institutions

You may submit (an) application(s) if your organization has any of the following characteristics:

- For-profit organizations
- Non-profit organizations
- Public or private institutions, such as universities, colleges, hospitals, and laboratories
- Units of State government
- Units of local government
- Eligible agencies of the Federal government
- Foreign Institutions
- Domestic Institutions
- Faith-based or community-based organizations

1.B. Eligible Individuals

Any individual with the skills, knowledge, and resources necessary to carry out the proposed research is invited to work with their institution to develop an application for support. Individuals from underrepresented racial and ethnic groups as well as individuals with disabilities are always encouraged to apply for NIH programs.

2. Cost Sharing or Matching

Not applicable

The most current Grants Policy Statement can be found at:
http://grants.nih.gov/grants/policy/nihgps_2003/nihgps_Part2.htm#matching_or_cost_sharing.

3. Other-Special Eligibility Criteria

Not applicable

Section IV. Application and Submission Information

1. Address to Request Application Information

The PHS 398 application instructions are available at http://grants.nih.gov/grants/funding/phs398/phs398.html in an interactive format. Applicants must use the currently approved version of the PHS 398. For further assistance contact GrantsInfo, Telephone (301) 435-0714, Email: GrantsInfo@nih.gov.

Telecommunications for the hearing impaired: TTY 301-451-0088.

2. Content and Form of Application Submission

Applications must be prepared using the most current PHS 398 research grant application instructions and forms. Applications must have a D&B Data Universal Numbering System (DUNS) number as the universal identifier when applying for Federal grants or cooperative agreements. The D&B number can be obtained by calling (866) 705-5711 or through the web site at http://www.dnb.com/us/. The D&B number should be entered on line 11 of the face page of the PHS 398 form.

The title and number of this funding opportunity must be typed on line 2 of the face page of the application form and the YES box must be checked.

3. Submission Dates and Times

Applications must be mailed on or before the receipt date described below (Section IV.3.A). Submission times N/A.

3.A. Receipt, Review and Anticipated Start Dates

Letter of Intent Receipt Date: N/A
Application Receipt Date(s): http://grants.nih.gov/grants/funding/submissionschedule.htm
Peer Review Date: http://grants.nih.gov/grants/funding/submissionschedule.htm
Council Review Date: http://grants.nih.gov/grants/funding/submissionschedule.htm
Earliest Anticipated Start Date: http://grants.nih.gov/grants/funding/submissionschedule.htm

3.A.1. Letter of Intent

A letter of intent is not required for the funding opportunity.

3.B. Sending an Application to the NIH

Applications must be prepared using the PHS 398 research grant application instructions and forms as described above. Submit a signed, typewritten original of the application, including the checklist, and five signed photocopies in one package to:

Center for Scientific Review
National Institutes of Health
6701 Rockledge Drive, Room 1040, MSC 7710
Bethesda, MD 20892-7710 (U.S. Postal Service Express or regular mail)
Bethesda, MD 20817 (for express/courier service; non-USPS service)

3.C. Application Processing

Applications must be **submitted on or before the application receipt dates** described above (Section IV.3.A.) and at http://grants.nih.gov/grants/dates.htm. Upon receipt, applications will be evaluated for completeness by CSR.

The NIH will not accept any application in response to this funding opportunity that is essentially the same as one currently pending initial review unless the applicant withdraws the pending application. The NIH will not accept any application that is essentially the same as one already reviewed. This does not preclude the submission of a substantial revision of an application already reviewed, but such application must include an Introduction addressing the previous critique.

Although there is no immediate acknowledgement of the receipt of an application, applicants are generally notified of the review and funding assignment within eight (8) weeks.

4. Intergovernmental Review

This initiative is not subject to intergovernmental review.

5. Funding Restrictions

All NIH awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm (see also Section VI.3. Reporting).

6. Other Submission Requirements

Specific Instructions for Modular Grant applications.

Applications requesting up to $250,000 per year in direct costs must be submitted in a modular budget format. The modular budget format simplifies the preparation of the budget in these applications by limiting the level of budgetary detail. Applicants request direct costs in

$25,000 modules. Section C of the research grant application instructions for the PHS 398 at http://grants.nih.gov/grants/funding/phs398/phs398.html includes step-by-step guidance for preparing modular budgets. Applicants must use the currently approved version of the PHS 398. Additional information on modular budgets is available at http://grants.nih.gov/grants/funding/modular/modular.htm.

Specific Instructions for Applications Requesting $500,000 (direct costs) or More per Year.

Applicants requesting $500,000 or more in direct costs for any year must carry out the following steps:

1) Contact the IC program staff at least 6 weeks before submitting the application, i.e., as you are developing plans for the study;

2) Obtain agreement from the IC staff that the IC will accept your application for consideration for award; and,

3) Include a cover letter with the application that identifies the staff member and IC who agreed to accept assignment of the application.

This policy applies to all investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended or revised version of these grant application types. Additional information on this policy is available in the NIH Guide for Grants and Contracts, October 19, 2001 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-004.html.

Plan for Sharing Research Data

The precise content of the data-sharing plan will vary, depending on the data being collected and how the investigator is planning to share the data. Applicants who are planning to share data may wish to describe briefly the expected schedule for data sharing, the format of the final dataset, the documentation to be provided, whether or not any analytic tools also will be provided, whether or not a data-sharing agreement will be required and, if so, a brief description of such an agreement (including the criteria for deciding who can receive the data and whether or not any conditions will be placed on their use), and the mode of data sharing (e.g., under their own auspices by mailing a disk or posting data on their institutional or personal website, through a data archive or enclave). Investigators choosing to share under their own auspices may wish to enter into a data-sharing agreement. References to data sharing may also be appropriate in other sections of the application.

Applicants requesting more than $500,000 in direct costs in any year of the proposed research must include a plan for sharing research data in their application. The funding organization will be responsible for monitoring the data sharing policy (http://grants.nih.gov/grants/policy/data_sharing).

The reasonableness of the data sharing plan or the rationale for not sharing research data may be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score.

Sharing Research Resources

Not Applicable

Section V. Application Review Information

1. Criteria

Only the review criteria described below will be considered in the review process

2. Review and Selection Process

Applications submitted for this funding opportunity will be assigned to the ICs on the basis of established PHS referral guidelines.

Appropriate scientific review groups convened in accordance with the standard NIH peer review procedures (http://www.csr.nih.gov/refrev.htm) will evaluate applications for scientific and technical merit.

As part of the initial merit review, all applications will:

- Undergo a selection process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed and assigned a priority score.
- Receive a written critique
- Receive a second level of review by the appropriate national advisory council or board

The following will be considered in making funding decisions:

- Scientific merit of the proposed project as determined by peer review
- Availability of funds
- Relevance of program priorities

The goals of NIH supported research are to advance our understanding of biological systems, to improve the control of disease, and to enhance health. In their written critiques, reviewers will be asked to comment on each of the following criteria in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that an application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

1. Significance. Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge or clinical practice be advanced? What will be the effect of these studies on the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field?

2. Approach. Are the conceptual or clinical framework, design, methods, and analyses adequately developed, well integrated, well reasoned, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

3. Innovation. Is the project original and innovative? For example: Does the project challenge existing paradigms or clinical practice; address an innovative hypothesis or critical barrier to progress in the field? Does the project develop or employ novel concepts, approaches, methodologies, tools, or technologies for this area?

4. Investigators. Are the investigators appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers? Does the investigative team bring complementary and integrated expertise to the project (if applicable)?

5. Environment. Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed studies benefit from unique features of the scientific environment, or subject populations, or employ useful collaborative arrangements? Is there evidence of institutional support?

2.A. Additional Review Criteria:

In addition to the above criteria, the following items will continue to be considered in the determination of scientific merit and the priority score:

Protection of Human Subjects from Research Risk: The involvement of human subjects and protections from research risk relating to their participation in the proposed research will be assessed (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Inclusion of Women, Minorities and Children in Research: The adequacy of plans to include subjects from both genders, all racial and ethnic groups (and subgroups), and children as appropriate for the scientific goals of the research will be assessed. Plans for the recruitment and retention of subjects will also be evaluated (see the Research Plan, Section E on Human Subjects in the PHS Form 398).

Care and Use of Vertebrate Animals in Research: If vertebrate animals are to be used in the project, the five items described under Section F of the PHS Form 398 research grant application instructions will be assessed.

2.B. Additional Review Considerations

Budget: The reasonableness of the proposed budget and the requested period of support in relation to the proposed research. The priority score should not be affected by the evaluation of the budget.

2.C. Sharing Research Data

Data Sharing Plan: The reasonableness of the data sharing plan or the rationale for not sharing research data may be assessed by the reviewers. However, reviewers will not factor the proposed data sharing plan into the determination of scientific merit or the priority score. The funding organization will be responsible for monitoring the data sharing policy. http://grants.nih.gov/grants/policy/data_sharing.

2.D. Sharing Research Resources

Not applicable

Section VI. Award Administration Information

1. Award Notices

After the peer review of the application is completed, the Principal Investigator will also receive a written critique called a Summary Statement.

If the application is under consideration for funding, NIH will request "just-in-time" information from the applicant. For details, applicants may refer to the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part4.htm).

A formal notification in the form of a Notice of Grant Award (NGA) will be provided to the applicant organization via electronic means. The NGA signed by the grants management officer is the authorizing document.

Selection of an application for award is not an authorization to begin performance. Any costs incurred before receipt of the NGA are at the recipient's risk. These costs may be reimbursed only to the extent considered allowable pre-award costs. See Also Section IV.5. Funding Restrictions.

2. Administrative and National Policy Requirements

All NIH grant and cooperative agreement awards include the NIH Grants Policy Statement as part of the notice of grant award. For these terms of award, see the NIH Grants Policy Statement Part II: Terms and Conditions of NIH Grant Awards, Subpart A: General (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_Part4.htm) and Part II Terms and Conditions of NIH Grant Awards, Subpart B: Terms and Conditions for Specific Types of Grants, Grantees, and Activities (http://grants.nih.gov/grants/policy/nihgps_2003/NIHGPS_part9.htm).

The following Terms and Conditions will be incorporated into the award statement and will be provided to the Principal Investigator as well as to the appropriate institutional official, at the time of award.

2.A. Cooperative Agreement Terms and Conditions of Award

Not applicable

3. Reporting

Awardees will be required to submit the PHS Non-Competing Grant Progress Report, Form 2590 annually (http://grants.nih.gov/grants/funding/2590/2590.htm) and financial statements as required in the NIH Grants Policy Statement.

Section VII. Agency Contacts

We encourage your inquiries concerning this funding opportunity and welcome the opportunity to answer questions from potential applicants. Inquiries may fall into three areas: scientific/research, peer review, and financial or grants management issues:

1. Scientific/Research Contacts:

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2. Peer Review Contact(s)

Not applicable

3. Financial or Grants Management Contacts:

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Section VIII. Other Information

Required Federal Citations

Use of Animals in Research:
Recipients of PHS support for activated involving live, vertebrate animals must comply with PHS Policy on Humane Care and Use of Laboratory Animals (http://grants.nih.gov/grants/olaw/references/PHSPolicyLabAnimals.pdf) as mandated by the Health Research Extension Act of 1985 (http://grants.nih.gov/grants/olaw/references/hrea1985.htm), and the USDA Animal Welfare Regulations (http://www.nal.usda.gov/awic/legislat/usdaleg1.htm) as applicable.

Human Subjects Protection:
Federal regulations (45CFR46) require that applications and proposals involving human subjects must be evaluated with reference to the risks to the subjects, the adequacy of protection against these risks, the potential benefits of the research to the subjects and others, and the importance of the knowledge gained or to be gained (http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm).

Data and Safety Monitoring Plan:
Data and safety monitoring is required for all types of clinical trials, including physiologic toxicity and dose-finding studies (phase I); efficacy studies (Phase II); efficacy, effectiveness and comparative trials (Phase III). Monitoring should be commensurate with risk. The establishment of data and safety monitoring boards (DSMBs) is required for multi-site clinical trials involving interventions that entail potential risks to the participants (NIH Policy for Data and Safety Monitoring, NIH Guide for Grants and Contracts, http://grants.nih.gov/grants/guide/notice-files/not98-084.html).

Sharing Research Data:
Investigators submitting an NIH application seeking $500,000 or more in direct costs in any single year are expected to include a plan for data sharing or state why this is not possible (http://grants.nih.gov/grants/policy/data_sharing).

Investigators should seek guidance from their institutions, on issues related to institutional policies and local IRB rules, as well as local, State and Federal laws and regulations, including the Privacy Rule. Reviewers will consider the data sharing plan but will not factor the plan into the determination of the scientific merit or the priority score.

Sharing of Model Organisms:
NIH is committed to support efforts that encourage sharing of important research resources including the sharing of model organisms for biomedical research (see http://grants.nih.gov/grants/policy/model_organism/index.htm). At the same time the NIH recognizes the rights of grantees and contractors to elect and retain title to subject inventions developed with Federal funding pursuant to the Bayh Dole Act (see the NIH Grants Policy Statement http://grants.nih.gov/grants/policy/nihgps_2003/index.htm). All investigators submitting an NIH application or contract proposal, beginning with the October 1, 2004 receipt date, are expected to include in the application/proposal a description of a specific plan for sharing and distributing unique model organism research resources generated using NIH funding or state why such sharing is restricted or not possible. This will permit other researchers to benefit from the resources developed with public funding. The inclusion of a model organism sharing plan is not subject to a cost threshold in any year and is expected to be included in all applications where the development of model organisms is anticipated.

Inclusion of Women And Minorities in Clinical Research:
It is the policy of the NIH that women and members of minority groups and their sub-populations must be included in all NIH-supported clinical research projects unless a clear and compelling justification is provided indicating that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43). All investigators proposing clinical research should read the "NIH Guidelines for Inclusion of Women and Minorities as Subjects in Clinical Research (http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-001.html); a complete copy of the updated Guidelines is available at http://grants.nih.gov/grants/funding/women_min/guidelines_amended_10_2001.htm. The amended policy incorporates: the use of an NIH definition of clinical research; updated racial and ethnic categories in compliance with the new OMB standards; clarification of language governing NIH-defined Phase III clinical trials consistent with the new PHS Form 398; and updated roles and responsibilities of NIH staff and the extramural community. The policy continues to require for all NIH-defined Phase III clinical trials that: a) all applications or proposals and/or protocols must provide a description of plans to conduct analyses, as appropriate, to address differences by sex/gender and/or racial/ethnic groups, including subgroups if applicable; and b) investigators must report annual accrual and progress in conducting analyses, as appropriate, by sex/gender and/or racial/ethnic group differences.

Inclusion of Children as Participants in Clinical Research:
The NIH maintains a policy that children (i.e., individuals under the age of 21) must be included in all clinical research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines" on the inclusion of children as participants in research involving human subjects (http://grants.nih.gov/grants/funding/children/children.htm).

Required Education on the Protection of Human Subject Participants:
NIH policy requires education on the protection of human subject participants for all investigators submitting NIH applications for research involving human subjects and individuals designated as key personnel. The policy is available at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-039.html.

Human Embryonic Stem Cells (hESC):
Criteria for federal funding of research on hESCs can be found at http://stemcells.nih.gov/index.asp and at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-02-005.html. Only research using hESC lines that are registered in the NIH Human Embryonic Stem Cell Registry will be eligible for Federal funding (http://escr.nih.gov/). It is the responsibility of the applicant to provide in the project description and elsewhere in the application as appropriate, the official NIH identifier(s) for the hESC line(s)to be used in the proposed research. Applications that do not provide this information will be returned without review.

Public Access to Research Data through the Freedom of Information Act:
The Office of Management and Budget (OMB) Circular A-110 has been revised to provide public access to research data through the Freedom of Information Act (FOIA) under some circumstances. Data that are (1) first produced in a project that is supported in whole or in part with Federal funds and (2) cited publicly and officially by a Federal agency in support of an action that has the force and effect of law (i.e., a regulation) may be accessed through FOIA. It is important for applicants to understand the basic scope of this amendment. NIH has provided guidance at http://grants.nih.gov/grants/policy/a110/a110_guidance_dec1999.htm. Applicants may wish to place data collected under this PA in a public archive, which can provide protections for the data and manage the distribution for an indefinite period of time. If so, the application should include a description of the archiving plan in the study design and include information about this in the budget

justification section of the application. In addition, applicants should think about how to structure informed consent statements and other human subjects procedures given the potential for wider use of data collected under this award.

Standards for Privacy of Individually Identifiable Health Information:
The Department of Health and Human Services (DHHS) issued final modification to the "Standards for Privacy of Individually Identifiable Health Information", the "Privacy Rule", on August 14, 2002. The Privacy Rule is a federal regulation under the Health Insurance Portability and Accountability Act (HIPAA) of 1996 that governs the protection of individually identifiable health information, and is administered and enforced by the DHHS Office for Civil Rights (OCR).

Decisions about applicability and implementation of the Privacy Rule reside with the researcher and his/her institution. The OCR website (http://www.hhs.gov/ocr/) provides information on the Privacy Rule, including a complete Regulation Text and a set of decision tools on "Am I a covered entity?" Information on the impact of the HIPAA Privacy Rule on NIH processes involving the review, funding, and progress monitoring of grants, cooperative agreements, and research contracts can be found at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-03-025.html.

URLs in NIH Grant Applications or Appendices:
All applications and proposals for NIH funding must be self-contained within specified page limitations. Unless otherwise specified in an NIH solicitation, Internet addresses (URLs) should not be used to provide information necessary to the review because reviewers are under no obligation to view the Internet sites. Furthermore, we caution reviewers that their anonymity may be compromised when they directly access an Internet site.

Healthy People 2010:
The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS-led national activity for setting priority areas. This PA is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.healthypeople.gov/.

Authority and Regulations:
This program is described in the Catalog of Federal Domestic Assistance at http://www.cfda.gov/ and is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review. Awards are made under the authorization of Sections 301 and 405 of the Public Health Service Act as amended (42 USC 241 and 284) and under Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. All awards are subject to the terms and conditions, cost principles, and other considerations described in the NIH Grants Policy Statement. The NIH Grants Policy Statement can be found at http://grants.nih.gov/grants/policy/policy.htm.

The PHS strongly encourages all grant recipients to provide a smoke-free workplace and discourage the use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, any portion of a facility) in which regular or routine education, library, day care, health care, or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

Loan Repayment Programs:
NIH encourages applications for educational loan repayment from qualified health professionals who have made a commitment to pursue a research career involving clinical, pediatric, contraception, infertility, and health disparities related areas. The LRP is an important component of NIH's efforts to recruit and retain the next generation of researchers by providing the means for developing a research career unfettered by the burden of student loan debt. Note that an NIH grant is not required for eligibility and concurrent career award and LRP applications are encouraged. The periods of career award and LRP award may overlap providing the LRP recipient with the required commitment of time and effort, as LRP awardees must commit at least 50% of their time (at least 20 hours per week based on a 40 hour week) for two years to the research. For further information, please see: http://www.lrp.nih.gov/.

Weekly TOC for this Announcement
NIH Funding Opportunities and Notices

Department of Health and Human Services

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